NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2004

PLAN FOR HIV-RELATED RESEARCH

IV: THERAPEUTICS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC ISSUES

Basic research on the pathogenesis and treatment of HIV disease continues to provide crucial insights leading to the discovery, development, and clinical testing of improved treatment regimens for HIV-infected individuals. The use of these therapies continues to result in the significant reduction of viral load, increased CD4 cell counts, decreased opportunistic infections, and improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with the antiretroviral drugs. A high priority is the development of better therapeutic regimens that are less toxic, limit the development of drug resistance, enter viral reservoirs to inhibit viral replication, promote easier adherence, and are more readily accessible. The global impact and continued spread of the AIDS pandemic in both developed and developing nations underscore the urgent need to develop therapeutic regimens which can be properly implemented in international settings.

The scientific agenda for therapeutics research is focused upon answering the following questions:

- Are there new viral and cellular targets against which therapies can be directed?
- What therapeutic agents can be developed that target drug resistant virus and have activity in viral compartments and cellular reservoirs?

- What are the optimal therapeutic approaches to the management of HIV infection, including when to start, change, sequence, or interrupt therapy?
- How can the pharmacologic properties of these agents be improved?
- What are the pharmacokinetics of these drugs in pregnant and breast-feeding women, and what impact does this have upon the fetus?
- What are the markers to predict the efficacy of immune-based therapies?
- What is the impact of co-infection upon disease progression and treatment of both HIV and the co-existing infection, such as hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), or malaria?
- What are the clinical and public health ramifications of antiretroviral treatment in developing countries?
- What types of interventions facilitate the delivery of therapeutic interventions for HIV disease in a resource-poor setting?

PRECLINICAL DEVELOPMENT OF NEW THERAPEUTIC AGENTS

PRIORITIES FOR FUTURE RESEARCH:

- **Advance the discovery and validation of new viral and cellular targets.**
- **Develop new therapeutic agents that:**
  - **target drug-resistant virus;**
  - **have activity in viral reservoirs and cellular compartments; and**
  - **have improved pharmacologic properties.**
- **Develop *ex vivo* and/or animal models to evaluate the biological properties of drugs, including their pharmacology and toxicology.**

NIH sponsors an active and comprehensive drug discovery and development program that permits the design and identification of new, safe, and more effective drugs that target drug-resistant virus, have activity in viral reservoirs and cellular compartments, and have improved pharmacologic properties. A priority of this program is the discovery and validation of new viral and cellular targets to direct the development of next generation and better therapeutic agents and regimens. Continued advances in therapeutics research demonstrate the need for Government- and industry-sponsored drug development research, preclinical development

of new agents, and clinical trials. The goal of this work is to develop therapeutic agents that not only slow disease progression, but also improve the quality of life and extend life expectancy for HIV-infected individuals in both developed and developing countries.

NIH-sponsored programs provide resources for conducting preclinical testing of potential compounds against HIV infection and its sequelae. The development of *ex vivo* and/or animal models to evaluate the biological properties of these drugs, as well as their pharmacology and toxicology, permits a better understanding of their potential role in the treatment armamentarium. The importance of these models is further emphasized by the increasing role of toxicities in causing significant morbidity and decreased quality of life, as well as interruption of therapies. Additional efforts are essential to accelerate the development and testing of microbicides and of other chemical and physical barriers to halt the sexual transmission of HIV and other sexually transmitted diseases (STDs). A separate component of this Plan has been developed for this critical area of NIH-sponsored research. Collaborations between Government-sponsored programs and the pharmaceutical and biotechnology industries are essential in advancing potential agents through this stage of drug development.

MOTHER-TO-CHILD TRANSMISSION INTERVENTION

PRIORITIES FOR FUTURE RESEARCH:

- **Develop therapeutic regimens to block mother-to-child transmission that can be implemented in developed and developing nations. Develop safe, effective, feasible, and conveniently administered strategies to interrupt mother-to-child transmission of HIV. Focus on international studies to inhibit mother-to-child transmission of HIV with special emphasis on breast-feeding.**
- **Evaluate the safety and pharmacokinetics of antiretroviral agents in pregnant and breast-feeding women, including studies on the transplacental passage of the agents and safety for the fetus.**
- **Evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn.**
- **Conduct studies to evaluate and reduce short- and long-term toxicity of antiretroviral drugs in women during pregnancy, and their offspring who were perinatally exposed.**

The continued development and testing of interventions to halt mother-to-child transmission, especially treatment regimens that can be implemented in developing nations, is a priority of NIH-sponsored AIDS

research. While there has been success in many developed nations, mother-to-child transmission continues to be a significant problem in developing countries and resource-poor settings. Advances are needed in identifying better treatment regimens that are capable of blocking mother-to-child transmission of HIV. A better understanding also is needed of the effects of these interventions upon the fetus, their short- and long-term toxicity potential, and their transplacental passage.

Significant advances have been made in the treatment, monitoring, and understanding of mother-to-child transmission since the success of the initial Pediatric AIDS Clinical Trials Group Protocol 076 using zidovudine chemoprophylaxis. Clinical studies are underway to answer many of the scientific questions that remain about the treatment of HIV infection during pregnancy. Some of these studies focus on the pharmacokinetics of antiviral agents in pregnant and breast-feeding women, as well as the transplacental passage of these agents. While preliminary studies suggest that the placental levels of these drugs may be higher (or lower) than maternal blood levels, the consequences of these levels, how drug dosing should be adjusted, and the short- and long-term consequences of these findings are unknown.

As the majority of mother-to-child infections are occurring in the developing world, treatment regimens that are safe, effective, feasible, and convenient are urgently needed to block this mode of transmission of HIV. The widespread use of antiretrovirals in these settings is further complicated by a complex array of challenges including co-infections and limited availability of health care staff and facilities, as well as limited capabilities for clinical and laboratory monitoring. Research on affordable regimens is essential, as are better methods for reducing HIV transmission through breast-feeding. Another important area for further study is the potential short- and long-term toxicities of these agents in both HIV-infected and uninfected offspring exposed perinatally and through breast-feeding to antiretroviral drugs.

DEVELOPMENT OF IMMUNOLOGY THERAPEUTICS

PRIORITIES FOR FUTURE RESEARCH:

- **Develop and evaluate therapeutic approaches that will improve and sustain immune function or prevent transmission of HIV infection.**
- **Identify and validate markers to predict the efficacy of immune-based therapies.**

High levels of viral replication occur during the initial burst of viral activity after HIV infection. Recent studies have provided additional

insights into the pathogenesis of HIV infection and into the role of individual immune factors in containing the infection. While the initiation of antiretroviral therapy (ART) has afforded improvements with restoration of immune function and improved immunologic parameters, further study is needed to determine what therapeutic approaches can improve and sustain immune function. The development of immunologic therapeutic approaches that can prevent transmission of HIV infection from infected individuals to uninfected individuals is important. Similarly, the identification of markers that will predict the efficacy of immune-based therapies is needed.

CLINICAL EVALUATION OF THERAPIES

PRIORITIES FOR FUTURE RESEARCH:

- **Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies.**
- **Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, adherence potential, and reduced cost.**
- **Target populations, especially women, injecting drug users (IDUs), children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial/ethnic differences.**
- **Enhance capabilities for long-term followup and evaluate the long-term effects of therapy, including delayed or late toxic effects.**
- **Conduct studies to determine the most medically advantageous time to initiate therapy and the implications of these findings on public health.**
- **Perform studies to evaluate the impact of treatment regimens to prevent HIV transmission.**
- **Identify treatment regimens that promote adherence and compliance.**

The widespread use of combinations of ART in HIV patient care in the United States and Western Europe since 1996 coincides with markedly decreased AIDS death rates and new AIDS cases, extended longevity, and substantial reductions in the incidence of AIDS-related opportunistic infections. While these significant gains have been made, ART has failed to eradicate HIV and a growing proportion of HIV-infected individuals receiving therapy fail to achieve a satisfactory reduction in viral load, develop drug-resistant strains of HIV, experience toxicities and metabolic side effects, and fail to comply with arduous treatment schedules. Thus, one of the

highest priorities of NIH-sponsored AIDS research remains the clinical evaluation of potential agents and development of treatment regimens against HIV infection and its associated opportunistic infections and malignancies. Clinical research targets the identification of better drugs and treatment regimens to reduce and overcome these limitations, so that HIV-infected individuals can live longer with improved quality of life and delayed disease progression.

In the United States, the AIDS epidemic continues to affect diverse communities including women, racial and ethnic minorities, adolescents, substance and alcohol abusers, and older adults. NIH continues to place a high priority on recruiting and retaining individuals from these affected populations in clinical trials to the extent that they reflect the ongoing epidemic. Increased enrollment of these communities may permit evaluation of potential differences in response to therapy due to gender and/or racial and ethnic differences.

Clinical trials permit the identification of effective treatment regimens with increased efficacy, decreased toxicity, improved pharmacokinetics, and activity in viral reservoirs that facilitate adherence. The metabolic and morphologic complications associated with these therapies present significant morbidity and warrant further investigation. These studies also will help define when to begin, switch, and interrupt drugs within treatment regimens and identify therapies for treatment-experienced individuals who no longer respond to the antiretroviral drugs that are currently available.

Clinical findings from NIH-sponsored studies are continuing to provide crucial information leading to better treatment regimens for HIV-infected individuals. The translation of clinical trial results into treatment guidelines and standards of care that can be used by health care providers is critical in bringing results from the "bench to the bedside" and, ultimately, resulting in better care for those affected by HIV disease.

EVALUATION OF CO-INFECTION

PRIORITIES FOR FUTURE RESEARCH:

- **Evaluate the effects of co-infection, especially with HBV, HCV, or TB, on the management of HIV. Determine the bidirectional effects of co-infection and treatments on disease progression and drug interactions.**
- **Develop new agents for the treatment of HBV, HCV, and TB in the setting of HIV infection, with specific attention to pharmacologic drug interactions and nonoverlapping toxicity.**

The alarming rates of HCV infection that are continuing to rapidly increase, and the continued expansion of the AIDS epidemic into substance abuse and minority communities, translate into greater numbers of co-infected individuals. NIH continues to place a priority on the evaluation of potential therapies for the prevention and treatment of HIV-associated infections and co-infections. A better understanding is needed to determine the bidirectional effects of co-infection and treatments for these co-infections on disease progression and drug interactions. In the international setting, hepatitis, TB, and malaria continue to play a significant role as co-morbidities in HIV infection. New drugs and drug regimens are needed for the treatment of HBV, HCV, and TB in the setting of HIV infection, with particular attention to drug interactions and minimizing toxicities.

INTERNATIONAL

PRIORITIES FOR FUTURE RESEARCH:

- **Expand international clinical research programs in countries with limited resources.**
- **Design and conduct clinical studies that are appropriate for diverse international settings.**
- **Design studies to improve and facilitate the delivery of therapeutic interventions for HIV disease.**
- **Evaluate the clinical and public health impact of antiretroviral treatment.**
- **Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for co-infections/opportunistic infections.**
- **Encourage studies that integrate therapeutic regimens and prevention interventions.**

NIH has placed a high priority on the conduct of international AIDS research and the development of treatment regimens to prevent, treat, and control HIV disease and its co-infections in developed and developing nations. These studies require the direct involvement of host nation researchers as equal partners in the design, conduct, and analysis of clinical trial protocols. This approach ensures the involvement of the host nation in the conduct of the clinical study as well as the implementation of therapeutic interventions after the study is completed. Two separate components of this Plan have been developed for the relevant areas of NIH-sponsored research: Training, Infrastructure, and Capacity Building, and International Research. The increasing urgency of the AIDS pandemic requires that treatment be viewed in the context of other complex and complicating factors: health care resources available, trained personnel and

infrastructure to provide these therapies, co-existing infections, and public health impact. While this represents a significant and daunting challenge, the development of safe, efficacious, and affordable treatment regimens must be targeted to all who are affected by HIV infection.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition, clearance, and prevention of transmission. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV transmission, infection, replication, and persistence.
(The scientific objectives of A and B are of equal weight.)

STRATEGIES:

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Develop agents (including natural products) and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
  - Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new compounds and chemical formulations, including microbicides and other methods, suitable for the genitourinary and gastrointestinal tracts.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent therapeutic agents with activity against drug-resistant strains. Post lead structures on publicly accessible databases in real time.
  - Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.

- Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish the infrastructure to provide services and reagents needed by the scientific community.
- Evaluate the intracellular pharmacokinetics and activity of antiretroviral agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
- Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.

- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.
  - Advance basic and applied gene-based strategies to treat HIV infection and its complications. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.
  - Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials. Investigate the use of pharmacogenetics in identifying optimum therapies.
  - Investigate the host cell effects of antiretroviral drugs.

OBJECTIVE - B:

Conduct clinical trials (including the development of new methodologies) to (1) evaluate the short- and long-term safety, efficacy, and effectiveness of therapeutic agents and strategies against HIV infection and transmission; (2) identify optimal and appropriate treatment modalities in treatment-naive and treatment-experienced HIV-infected individuals; and (3) define, evaluate, and mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Encourage clinical trial designs that build on epidemiologic studies that advance the understanding of disease pathogenesis and progression. Develop appropriate partnerships to design and conduct clinical studies of regimens appropriate for domestic and international settings.
(The scientific objectives of A and B are of equal weight.)

STRATEGIES:

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and strategies for individuals who have acute or recent infection, chronic infection but no prior antiretroviral therapy, and those with prior antiretroviral therapy including individuals with multiple drug-resistant virus.
  - Support clinical trials to study
    - the long-term efficacy (including toxicities) of therapeutic strategies,
    - the timing, selection, and strategic sequencing of antiretroviral agents to optimize clinical outcome, and
    - the effects of structured treatment interruption on virologic, immunologic, and clinical outcome.

- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials that reflect the demographics of the epidemic, including traditionally underrepresented populations. When appropriate, evaluate potential gender, race, ethnicity, age-specific, and pregnancy-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.
  - Identify and evaluate the viral and host factors, including human genomics, associated with antiretroviral treatment failure including malabsorption, drug interactions, drug resistance, drug toxicities, pharmacogenetics, and suboptimal adherence.
  - Support clinical trials to evaluate the safety and efficacy of gene therapy.
  - Support studies that combine novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.
- Encourage and facilitate the study of co-formulated antiretrovirals. Encourage cooperation of the private sector/industry in this effort.
- Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with antiretroviral therapy.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate the prognostic value of surrogate markers in response to various therapeutic interventions.
- Design, test, and evaluate methods to improve the retention of individuals in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of antiretroviral agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Develop methodology for research on the ethical conduct of clinical trials.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management.

- Investigate drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals.

Viral Reservoirs

- Evaluate the presence and persistence of HIV in different tissue compartments during ART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.

- Evaluate the penetration of antiretroviral drugs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, etc.).

Viral Resistance and Fitness

- Explore the utility of real-time antiretroviral phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.

- Evaluate the impact of transmission of drug-resistant HIV strains on disease progression and therapy.

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to antiretroviral regimens.

- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.

Co-infection with Hepatitis B Virus and/or Hepatitis C Virus

- Evaluate the bidirectional effects of co-infection with HBV and/or HCV in HIV-infected individuals. Evaluate the impact of ART on reactivation of hepatitis viruses, treatment of viral hepatitis in co-infected individuals, transmission of hepatitis viruses, and development of late-stage complications of viral hepatitis.

International

- Enhance the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children.
- Assist developing nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of antiretroviral agents and other therapies in local settings.
- Assess the barriers to delivery of effective HIV/AIDS health care including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop simpler, reliable, user-friendly, and inexpensive assay technologies for monitoring immunologic and virologic status and antiretroviral drug responses that can be used in resource-poor settings.
- Develop standardized clinical indicators to determine when to initiate antiretroviral drug therapy, to monitor response to therapy, and to determine when to change therapy.
- Evaluate other simple and inexpensive surrogate markers of immunologic and virologic responses for use in resource-poor settings.
- Determine acceptable laboratory monitoring for drug toxicity in resource-poor settings.

OBJECTIVE - C:

Develop strategies to evaluate, prevent, and treat ART-related complications with special emphasis on metabolic and body composition changes.

STRATEGIES:

- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens as well as during chronic treatment.
- Support research on the pathogenesis and mechanisms of the complications of therapeutic regimens used to treat HIV disease and its associated disorders.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or suppression of HIV replication may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, and bone studies into ongoing and planned treatment trials, including structured treatment interruption studies, which may provide an opportunity to answer important questions related to potential complications of ART.
- Develop approaches to monitor and evaluate the effects of gender/race and age on complications of ART.
- Evaluate the impact of nutritional deficits, impaired access to safe drinking water, regionally significant co-infections, and other population- and area-specific factors on complications of ART in developing countries.
- Support research on the interactions of antiretroviral treatment on co-infections.

OBJECTIVE - D:

Develop and evaluate new agents and strategies for preventing and treating HIV-associated infections and co-infections, especially HBV, HCV, TB, human papillomavirus (HPV), human herpesvirus 8/Kaposi's sarcoma associated herpesvirus (HHV-8/KSHV), malaria, and other diseases prevalent in international settings.

STRATEGIES:

Preclinical Discovery and Development

- Identify and validate potential molecular targets for the discovery and development of agents for prevention and treatment of HIV-associated infections. Delineate the structure and function of potential molecular targets of HIV-associated opportunistic infections (OIs).
- Support preclinical drug design and development programs to develop therapies against associated pathogens, especially *Pneumocystis*, Cryptosporidium, *Mycobacterium avium* complex (MAC), *Mycobacterium tuberculosis*, Candida, microsporida, JC virus (JCV, the etiologic agent of progressive multifocal leukoencephalopathy [PML]), cytomegalovirus (CMV), HPV, HHV-8, azole-resistant fungi, and other prominent co-infections such as hepatitis B and hepatitis C, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating OIs; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Cooperate with the private sector to increase involvement and investment in OI drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

Clinical Trials of Therapeutic Regimens

- Assess the impact of new antiretroviral regimens on the risks for and manifestations of infections associated with HIV/AIDS in adults, adolescents, and children.
- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.

- Support clinical research in the context of drug abuse treatment to reduce HIV-associated infections among HIV-infected drug users.

Clinical Trial Methodology

- Improve strategies for prevention of multiple infections in the context of antiretroviral treatment; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.

- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs, to improve the efficiency of clinical trial design and the risk/benefit ratio of the currently utilized drugs for prophylaxis and for treatment.

- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs, quantitative assessment of microbiological responses, and drug sensitivity testing.

Co-infections

- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.

- Support clinical trials, domestic and international, of individuals co-infected with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in co-infected individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression (late versus middle versus advanced HIV disease).

- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in co-infected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.

- Support clinical trials investigating the efficacy and risks of treatment of hepatitis C in individuals who are co-infected with HIV and HCV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.

- Study the interaction of co-infections with HIV transmission (e.g., placental malaria and perinatal infection) and effects on HIV disease progression.

Pharmacology and Toxicology

- Conduct preclinical studies of anti-OI drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity.
- Support clinical studies to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs in HIV-infected infants, children, and pregnant women.
- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against multiple drug-resistant TB (MDR-TB).

Adherence

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-co-infection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.

International

- Conduct clinical trials to evaluate agents for the prophylaxis and treatment of HIV-associated OIs; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.

OBJECTIVE - E:

Develop, evaluate, and implement strategies for interrupting mother-to-child transmission applicable to resource-rich and -poor countries, including strategies to interrupt transmission through breast-feeding and evaluation of short- and long-term effects of these interventions on women and infants.
(The scientific objectives of E and F are of equal weight.)

STRATEGIES:

Mechanisms of Transmission

- Investigate the mechanisms and timing of mother-to-child HIV transmission (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease mother-to-child transmission or provide alternatives to currently identified effective strategies.
- Investigate risk factors for breast milk associated with early and late HIV transmission (e.g., breast milk viral load, immune factors, mastitis, and exclusive versus mixed breast-feeding).
- Evaluate the influence of pre-existing viral drug resistance in pregnant women on the efficacy of antiretroviral regimens to prevent mother-to-child transmission.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.
- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum transmission of HIV, and to evaluate transplacental passage of antiretroviral agents and their effects on placental function and on fetal development and viability.

Interventions to Reduce Transmission

- Develop safe and conveniently administered strategies to interrupt mother-to-child transmission of HIV using interventions that are affordable in resource-poor nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.

- Evaluate strategies for reducing mother-to-child HIV transmission when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Develop and evaluate strategies for implementation of effective prevention interventions in resource-poor and -rich countries.
- Support international collaborative efforts to conduct clinical trials of interventions to interrupt mother-to-child transmission of HIV.
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring without compromising treatment of the pregnant women; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Study the effects of antiretroviral regimens used for maternal health indications on the risk of vertical transmission (including postnatal transmission through breast milk) and other outcomes, including pregnancy outcome.

Issues Related to Antiretroviral Interventions

- Evaluate the toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and antiretroviral activity of new agents, existing agents, and combinations of agents in pregnant women and their neonates.
- Evaluate the risk for the development of drug-resistant virus in pregnant women with use of short and/or longer-course antiretroviral prophylaxis regimens, and its effect on vertical transmission, as well as maternal and infant health.
- Support the long-term followup of women treated for HIV infection during pregnancy and/or treated for a short period of time postpartum to reduce transmission through breast milk, particularly those who otherwise could have deferred initiating treatment, chosen to discontinue treatment after delivery, or received postnatal prophylaxis for transmission through breast milk, for durable clinical responses as well as safety evaluations.

- Support the long-term followup of children exposed to ART during pregnancy and/or postpartum to evaluate possible late effects of this exposure.

- Evaluate the potential mechanism for possible carcinogenic or mutagenic effects of *in utero* antiretroviral exposure.

- Investigate interactions between HIV therapeutics and drugs of abuse as well as medications used for the treatment of substance abuse in pregnant women; evaluate the impact of such interactions on drug abuse therapy and on vertical transmission of HIV.

Clinical Trials and Other Interventions

- Further evaluate the risks and benefits of cesarean delivery for reducing transmission (e.g., evaluate the risk of postpartum morbidity in infected women with elective cesarean delivery and determine whether the additional benefit of cesarean delivery for preventing transmission accrues in women receiving ART).

- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the treatment of HIV-infected pregnant women and their offspring.

- Develop, incorporate, and validate appropriate quality-of-life parameters and methods to measure antiretroviral drug adherence in clinical trials of HIV-infected pregnant women.

Implementation Issues

- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in resource-poor and -rich settings to permit the earliest possible determination of HIV infection in infants, and whether antiretroviral and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor and to assess the acceptability of such testing and peripartum antiretroviral prophylaxis to the women.

- Conduct clinical, operational, and health services research relevant to improving health outcomes in HIV-infected mothers and their children.

OBJECTIVE - F:

Evaluate the impact of antiretroviral and immunotherapeutic strategies and their roles in the prevention of HIV transmission. (The scientific objectives of E and F are of equal weight.)

STRATEGIES:

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of antiretroviral regimens to prevent sexual transmission.
- Use and/or develop suitable animal models to evaluate genital and anal passage of antiretroviral agents.

Interventions to Reduce Transmission

- Support international collaborative efforts to conduct trials of antiretroviral, immunotherapeutic, and other treatment interventions with an endpoint of sexual transmission.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, and microbicides, alone or in combination.

Issues Related to Antiretroviral Interventions

- Evaluate the risk for the development of antiretroviral drug resistance in sequestered genital and anorectal sites with use of short and/or longer-course antiretroviral prophylaxis regimens, and therapeutic regimens that involve cycling on and off antiretroviral drugs and their impact on sexual transmission of HIV.
- Evaluate the public health impact of regimens to reduce viral load on sexual transmission.
- Evaluate the public health impact of treatment interruptions on HIV transmission.

OBJECTIVE - G:

Develop and evaluate therapeutic approaches, including therapeutic vaccine candidates, that will restore and sustain a competent immune system in HIV-infected individuals.

STRATEGIES:

- Employ approaches to immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that might be used in resource-poor settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches for HIV infection and its sequelae, including the testing of optimum immunogens; determine best patient disease status for response, most effective immunization dose and schedule, and most meaningful read-out of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.
- Evaluate the immune system after partial restoration by effective ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents including the use of vaccines for specific OIs.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.

- Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and co-receptors and thus inhibit entry into cells.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate markers that may identify individuals at risk for late complications of therapy.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials.
- Evaluate treatment interruption both to stimulate HIV-specific immune response (structured treatment interruption [STI]) and as an analytic read-out of treatment effect (analytic treatment interruption [ATI]).
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.
- Evaluate immune-based therapies for the purpose of improving ART-sparing regimens, permitting delay in initiating or reinitiating ART in regimens of scheduled intermittent therapy (SIT).

OBJECTIVE - H:

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system disorders in HIV-infected individuals.
(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

- Develop and evaluate novel strategies and agents, such as neuroprotective agents, that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Design and conduct clinical trials addressing nervous system complications of HIV infection in adults, adolescents, and children.
- Determine the incidence and prevalence of HIV-associated neurologic disease after long-term ART.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of treatment effects.
- Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; evaluate their safety and efficacy in clinical trials.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of antiretroviral drugs into the CNS compartment.
- Develop better strategies including complementary and alternative medicine therapies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected individuals.

- Characterize the CNS pharmacokinetics and pharmacodynamics of antiretroviral drugs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and co-occurring mental health disorders.
- Validate and enhance the efficiency of neuropsychological and neurologic tests performed in the context of clinical trials to identify those tests most capable of determining treatment-related changes in different age and racial/ethnic groups.
- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies for pain management.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease in clinical trials.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic complications of HIV disease.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of the nervous system complications of HIV infection in clinical trials.
- Selectively incorporate neurologic and neuropsychological assessments into HIV-related clinical trials.

OBJECTIVE - I:

Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of HIV-associated cancers. (The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

Pathogenesis Research and Preclinical Drug Development

- Identify novel mechanisms and targets (e.g., cytokines, angiogenesis factors, and hormones) for treatment and prevention of HIV-associated tumors such as KS, non-Hodgkin's lymphoma (NHL), and HPV malignancies, including anogenital dysplasias and cancers; develop new therapeutic strategies based on these findings.
- Develop *in vitro* models of KS and assays for angiogenesis inhibitors.
- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Based upon structural biologic and biochemical information, develop therapeutic agents for the treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models (e.g., severe combined immunodeficiency-human [SCID-hu] mice) for the testing of potential therapeutic strategies against HIV-associated malignancies.

Diagnostic Methods

- Improve methods for early diagnosis of malignancies and for early detection of recurrent cancer.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, Epstein-Barr virus [EBV], HPV, and HBV) in their pathogenesis.
- Evaluate novel approaches for the treatment of HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.

- Support approaches using gene-based technologies, such as tissue array and microarray in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses with clinical benefit, including quality-of-life parameters; develop a staging system indicative of prognostic response and survival.
- Encourage collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected individuals with non-AIDS-defining malignancies. Evaluate the impact of therapy upon virologic, immunologic, tumor parameters, and drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- Study the role of *in utero* exposure to antiretroviral drugs on the risk of later development of tumors, in both uninfected and infected children born to HIV-infected women who received antiretroviral drugs during pregnancy.
- Study populations in resource-poor settings at increased risk of AIDS-related malignancies due to endemic infectious agents (e.g., HHV-8) and HPV-associated cervical cancer in women.

OBJECTIVE - J:

Develop and evaluate strategies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, and hematologic, dermatologic, renal, metabolic, pulmonary, cardiac, gastrointestinal, bone and musculoskeletal, endocrinologic, psychiatric, and oral manifestations.
(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection.
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of complementary and alternative medicine therapies, including nonpharmacologic interventions such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its complications.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the interactions between antiretroviral agents and psychotropic medications; develop strategies to avoid or minimize the clinical impact of these interactions.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2004 OAR Planning Group for Therapeutics

FY 2004 THERAPEUTICS PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ARV	antiretroviral
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CIPRA	Comprehensive International Programs for Research on AIDS
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
ddI	dideoxyinosine
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GBV-C	GB virus (hepatitis G)

GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria
GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission

N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization
NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NMAC	National Minority AIDS Council
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
OPHS	Office of Public Health and Science
PBMC	peripheral blood mononuclear cell
PCP	*pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trial
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis

Th	T helper cells
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
WRAIR	Walter Reed Army Institute for Research